

Essential Prescribing Information (EPI)

1. Introduction and Background Information

CAUTION: Federal (USA) Law restricts this device to the sale by or on the order of a physician (or properly licensed practitioner).

1.1. Device Description

OSTEOSPACE is a quantitative ultrasound bone sonometer (QUS) which measures bone properties at the calcaneus using non-audible high frequency sound waves. The device consists of the scanner, standard PC and accessories. The scanner consists of a footwell to position the foot and two ultrasound transducers that contact the heel so that ultrasound beam is passed through it.

The OSTEOSPACE measurements are made with the patient seated in a chair without wheels in front of the device and his/her foot is placed into the foot-well. The heel is smeared with standard water-soluble ultrasound gel; the gel is the optimum medium for the transmission of ultrasound. The transducers are positioned with the aid of a low power laser onto the external part of the maleolus. The transducers are then brought into contact with the heel. A transducer on one side of the heel converts an electrical signal into a sound wave which passes through the patient's heel. The second transducer on the opposite side of the patient's heel receives the sound wave and converts it into an electrical signal that is analyzed by the OSTEOSPACE software. Region of interest (ROI), 14 mm diameter circle, is automatically selected and scanned.

The results are expressed in broadband ultrasound attenuation (BUA) measured as dB/MHz. This ultrasound parameter is based on frequency dependent attenuation where higher BUA values correspond to lower risk of fracture and vice versa.

Before the BUA measurement can be used for a diagnosis it needs to be compared to the average value of young normal Caucasian females (ages 20 to 39). This comparison is done using an index called a T-score, which represents the BUA value on a normalized scale. T-score above (below) zero corresponds to a bone stronger (weaker) than that of the average young normal Caucasian women. The T-score is the recommended parameter for assessing the risk of fracture.

Comparing the actual BUA value to the average value in a healthy population of the same gender, ethnic origin, and age, when expressed in terms of standard deviation (SD) of that population, is called Z-score, which can be used as an aid in the detection of conditions associated with non age-related bone loss.

1.2. Indications for use

The OSTEOSPACE is a quantitative ultrasound bone sonometer device (QUS) to be used for the measurement of broadband ultrasound attenuation (BUA) of the calcaneus, as an aid, together with other clinical risk factors, to diagnose osteoporosis and other medical conditions leading to

reduced bone strength and to estimate the risk of subsequent atraumatic fracture. The output is expressed in terms of BUA, T-score, and Z-score.

1.3. Contraindications

None.

1.4. Warnings

- a) The OSTEOSPACE should not be used on subjects with breached skin, abrasion, or open sores on the skin area that comes into contact with the probe.
- b) The OSTEOSPACE should not be used on a foot with edema (excess water/swelling).
- c) The OSTEOSPACE should not be used on patients with leg paralysis or lower extremity prosthesis.
- d) Patients must not move their foot during the scanning operation. Such movement can cause inaccuracies in both the image and the BUA measurement.

1.5. Precautions

- a) Users should read the Operators Manual before prescribing OSTEOSPACE, or interpreting the results. OSTEOSPACE should always be switched ON/OFF using the Main Switch located at the rear of the Scanner.
- b) Do NOT individually switch off the PC, the Monitor, or the Printer.
- c) Do not use on patients under the age of 20 years old, as there is no reference database available for this age group.
- d) Use the OSTEOSPACE only indoors, in a clean dry environment. Failure to do so could result in unsatisfactory results.
- e) Do not store the OSTEOSPACE or the Phantom near either a heat source or air conditioner.
- f) Do not use this equipment in the presence of a flammable anaesthetic, oxygen, or nitrous oxide.
- g) The OSTEOSPACE must not be cleaned with abrasive materials, as this will cause damage to the ultrasound probes.
- h) All interfacing equipment (monitor, printer) must meet with IEC 60601 or equivalent electrical standards.
- i) Do not use portable cellular equipment (walkie-talkies, radio phones, portable telephones) in the proximity of the OSTEOSPACE during its operation, as this may impact the accuracy of the measurements.
- j) Use only FDA approved water soluble ultrasound gel with OSTEOSPACE.
- k) Regularly inspect the silicone pads on the faces of the ultrasonic transducers for cracks or other signs of degradation.
- l) Don't stare directly into a laser beam.
- m) After applying ultrasound gel to the patient and transducers wash hands or wear gloves before touching the equipment or computer.
- n) In order to avoid electrical shocks, do not remove the cover from the OSTEOSPACE. The OSTEOSPACE contains no user-serviceable parts.

- o) The OSTEOSPACE requires proper cleaning and disinfection between each patient use to help prevent transmission of infection between patients.
- p) Clean and disinfect the OSTEOSPACE footwell, calf support, ultrasonic transducers and inserts and wipe dry with a clean cloth or towel, or allow to air dry.
- q) Protective gloves should be worn during cleaning and disinfecting procedures.
- r) Soiled materials should be disposed of in appropriate waste receptacles.

1.6. Adverse events

None reported.

1.7. Maintaining device effectiveness

The physician / operator should routinely clean the OSTEOSPACE with non abrasive materials. The Quality Control test is carried out each day by the operator with an external phantom provided with the scanner. Graphic and statistic display of the results can be accessed from the main menu. The physician / operator should not attempt to access the internal parts of the device.

1.8. Patient counseling information

Supplied with the OSTEOSPACE are Patient Brochures titled "Information for Patients". These documents can be freely duplicated or can be ordered from MEDILINK.

Further information on osteoporosis can be obtained from the *National Osteoporosis Foundation*, 1150 17th Street, N. W. Suite 500, Washington, D. C. 20036-4603, Tel : (202) 223-2226.

1.9. How the OSTEOSPACE is supplied

OSTEOSPACE operates with a computer and other accessories.

The computer, monitor, and printer may be supplied by either the customer, the distributor or by MEDILINK. MEDILINK will provide the specifications for the above components when the components are to be provided by the user or distributor.

2. Clinical Studies

Clinical studies were conducted to assess the safety and effectiveness of the OSTEOSPACE, a quantitative ultrasound bone sonometer device, as an aid to establish the diagnosis of osteoporosis and to identify patients with high risk of osteoporotic fracture. Clinical studies were carried out in two U.S. centers, the University of Massachusetts (UMASS) and the University of California (UCSF), San Francisco, and in one European center, the Geneva University Hospital (HUG), Switzerland. The same protocol was followed in all the centers.

2.1 Reference Database Study

Objective: This study was to establish a U.S. Reference Database (Normality curve) for the BUA of OSTEOSPACE on healthy or non-fractured Caucasian U.S. women aged 20 to 79.

Methods: Four hundred ten (410) healthy Caucasian U.S. females, ranging in age from 20 to 79 years, were measured using the OSTEOSPACE to establish the normality curve.

Results: BUA was found statistically independent of age for 235 females ranging from 20 to 47. Thus, over this period, the reference curve could be represented as a constant equal to the average BUA over the group ($BUA_{20-47} = 66.16$ dB/MHz). Over 47 years old, a 3rd order polynomial regression was found to fit the best.

Conclusions: The Normality Curve of OSTEOSPACE[®] BUA for Caucasian U.S. Women displayed in Figure 1 shows that between the age of 48 and 60 years (post menopause), the BUA significantly declined by 3.5 dB/MHz (approximately 83% of the total range). Then, from 60 and 79 years old, the BUA further declined by 0.7 dB/MHz, i.e. approximately 17% of the range.

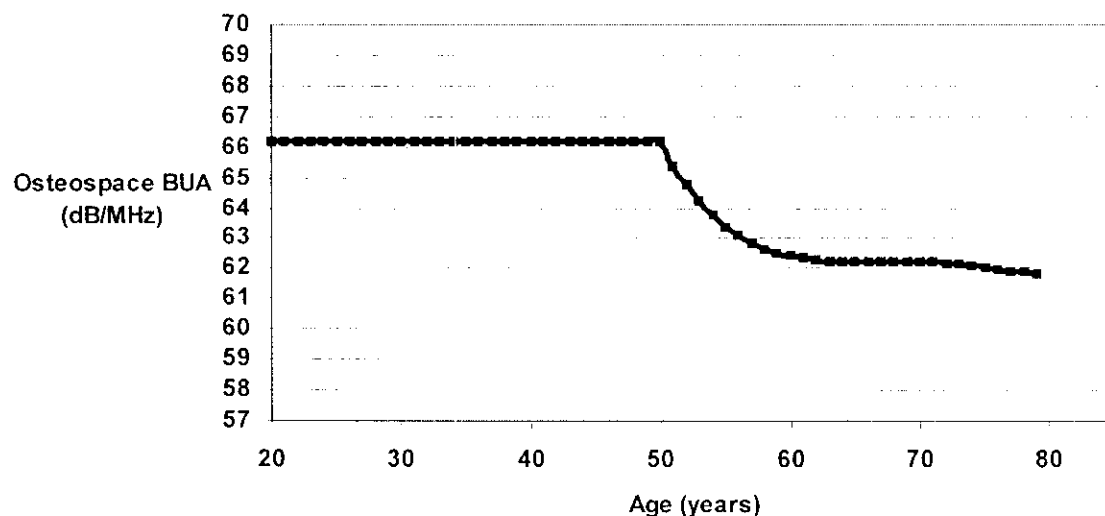


Figure 1- Normality Curve of OSTEOSPACE BUA for Caucasian U.S. Women

The World Health Organization (WHO) criterion for T-score is the difference between the patient's measurement and the mean of a healthy young female Caucasian reference population between the ages of 20 and 39 expressed as the number of standard deviations for the reference database, between the two values. The reference population for this device shows that there was no difference between using 20-39 group and 20-47 group. However, the 20-39 age range was selected for the representative sample of the young normal Caucasian U.S. female reference population

to maintain consistency with the WHO definition. This young reference population's mean BUA, as well as its standard deviation (SD), were calculated for the purpose of generating T-scores (see Table 1).

	Value (dB/MHz)	95% Confidence Interval
Mean BUA OSTEOSPACE	66.16	65.5 - 66.8
Standard Deviation	4.6	3.8 - 5.4

Table 1- Young Reference Value for OSTEOSPACE BUA (Data From 171 U.S. Caucasian Females, Ages 20 to 39)

Given the previous results, the T-score of the patient "j" is calculated as follows:

$$T\text{-score}_j = \frac{BUA_j - 66.16}{4.6} \quad \text{where } BUA_j \text{ is the BUA measured on the patient "j".}$$

2.2 Precision Study

Objective: To estimate the in-vivo short-term precision of the BUA measurements obtained by OSTEOSPACE

Methods: Fifty-six (56) subjects ranging in age from 20 to 79 were recruited by UMASS and UCSF the two U.S. centers and used to assess the measurement reproducibility. Each subject was examined three times with Osteospace, with foot repositioning before each examination.

Results: Precision was evaluated by calculating the RMS SD (Absolute Precision), the RMS CV(Relative Precision), the CV, the SCV(Standardized Coefficient of Variation) and the TSD(Standard Deviation of the T-score). (See section 17 of the User Manual for definitions). Results are displayed in Table 2.

	BUA OSTEOSPACE
RMS SD	1.19dB/MHz
RMS CV	1.84 %
CV	1.31 %
SCV	3.97 %
TSD	0.26

Table 2- Results of the Evaluation of the OSTEOSPACE Precision (56 American Subjects Aged between 20 to 79)

Conclusions: The CVs for the OSTEOSPACE measurements show that the device can provide precise measurements of BUA.

2.3. Fracture Risk Studies

Objective:: To establish the capability of OSTEOSPACE BUA, a) to assess the risk of fracture, b) to discriminate between patients who have suffered atraumatic fractures and age-matched control subjects who have never had an atraumatic fracture, and c) to compare the performance of the device with those of one DEXA (Hologic QDR 4500®) and two sonometer systems (Lunar ACHILLES+® and Hologic SAHARA®), in order to assess possible bias in selection of control patients ("Fracture Risk Studies"). The output of the QDR 4500 is bone density. The output of the ACHILLES+® is Stiffness and the SAHARA® is the Quantitative Ultrasound Index (QUI).

Methods: In order to assess the capacity of OSTEOSPACE to evaluate the risk of fracture and to discriminate the Osteoporotic patients, fractured subjects and age-matched controls were enrolled by the HUG and UCSF centers. UCSF measured 52 age-matched controls and 50 fractured patients. HUG measured 43 age-matched controls and 56 fractured patients. Subjects were measured using the OSTEOSPACE (both sites), Hologic QDR 4500® (UCSF only), Lunar ACHILLES+® (HUG only) and the Hologic SAHARA® (HUG only).

Results: Table 3 shows that the BUA results for the fractured group expressed in T-score or in Z-score are similar to neck or spine BMD.

	Controls	Fractured	Z-score	T-Score
BUA OSTEOSPACE	62.6 ± 4.5	58.8 ± 4.9	-0.9	-1.6
Neck BMD (QDR 4500®)	0.695 ± 0.111	0.614 ± 0.111	-0.7	-2.1
Spine BMD (QDR 4500®)	0.960 ± 0.145	0.839 ± 0.141	-0.8	-1.9

Table 3- UCSF Center, OSTEOSPACE and DEXA Parameters of the Two Groups Expressed in Z-score and T-score

Table 4 shows that the OSTEOSPACE measurements for the fractured subjects, when expressed in T-score or in Z-score, are similar to the QDR 4500® neck or spine BMD, or to Hologic QUI and Lunar Stiffness results.

	Controls	Fractured	Z-score	T-Score
BUA OSTEOSPACE	61.2 ± 5.0	55.8 ± 5.2	-1.1	-2.3
QUI (SAHARA®)	73.9 ± 15.3	59.8 ± 19.4	-0.9	-2.2
Stiffness (ACHILLES+®)	71.0 ± 11.3	58.6 ± 12.5	-1.1	-1.8

Table 4- HUG Center, OSTEOSPACE and QUS Parameters for the Two Groups Expressed in Z-score and in T-score

For each center, non-adjusted and adjusted Odds Ratios per standard deviation decrease were estimated, with their 95% confidence intervals, and the areas under the ROC curves were obtained (see Tables 5 and 6).

	Non-Adjusted Odds Ratios (95% CI)	Adjusted Odds Ratios* (95% CI)	Area under the ROC Curve** (95% CI)
BUA OSTEOSPACE	2.44 (1.49 - 3.98)	1.80 (1.05 - 3.10)	0.72 (0.62 - 0.82)
Neck BMD (QDR 4500®)	2.30 (1.40 - 3.79)	1.70 (1.02 - 2.99)	0.71 (0.60 - 0.81)
Spine BMD(QDR 4500®)	2.47 (1.53 - 3.98)	2.32 (1.36 - 3.93)	0.74 (0.64 - 0.84)

*Adjusted by Age, Weight and Height.

**Not Adjusted by age.

Table 5- UCSF Center, Odds Ratios per Standard Deviation Decrease and Area under the ROC Curve for each Bone Parameters

	Non-Adjusted Odds Ratios (95% CI)	Adjusted Odds Ratios* (95% CI)	Area under the ROC Curve** (95% CI)
BUA OSTEOSPACE	3.04 (1.81 - 5.10)	2.91 (1.57 - 5.37)	0.77 (0.68 - 0.86)
QUI (SAHARA®)	2.47 (1.46 - 4.17)	1.88 (1.05 - 3.34)	0.77 (0.68 - 0.86)
Stiffness (ACHILLES+®)	3.17 (1.83 - 5.47)	2.56 (1.39 - 4.73)	0.77 (0.68 - 0.86)

*Adjusted by Age, Weight and BMI.

**Not Adjusted by age.

Table 6- HUG Center, Odds Ratios per Standard Deviation Decrease and Area under the ROC Curve for each Bone Parameters

Conclusions: ROC curves as well as Odds Ratios analysis showed no statistical difference between OSTEOSPACE®, DEXA, and QUS measurements, thus demonstrating the absence of

any significant bias in selection of control patients, and also demonstrating the ability of the Osteospace to discriminate between fractured subjects and controls.

3. Individualization of treatment

The OSTEOSPACE is suitable for T-score determinations of adults of any ethnicity, age or gender, however all patients are to be referred to the young normal Caucasian U.S. female reference database. The OSTEOSPACE is suitable for Z-score determinations of Caucasian women only, since this is the only reference database provided, and since Z-score, unlike T-score, requires comparison to non-fractured subjects of the same age, ethnicity, and gender.

4. System safety / Conformance to standards

The OSTEOSPACE conforms to International Standards for safety and electromagnetic compatibility. This device uses ultrasound power levels lower than standard ultrasound devices which are widely used and accepted. See 4.2 Ultrasound radiation below.

4.1. Voluntary standard compliance

OSTEOSPACE complies with:

IEC 60601-1 (General requirements for electrical safety)

IEC 60601-1-2 (General requirements for electromagnetic compatibility)

4.2. Ultrasound radiation

Four ultrasound probes were tested and the acoustic output values are specified below.

	SERIAL NUMBER				Typical Uncertainty (+/-)
	Probe 1	Probe 2	Probe 3	Probe 4	
MI	0.068	0.070	0.069	0.064	± 12 %
$P_{r,3}$ (MPa)	86×10^{-3}	88×10^{-3}	87×10^{-3}	81×10^{-3}	± 10 %
I_{SPPA} (W/ cm ²)	0.40	0.45	0.47	0.43	± 27%
I_{SPTA} (mW/ cm ²)	4.2×10^{-3}	4.4×10^{-3}	4.3×10^{-3}	4.1×10^{-3}	± 25%
Beam diameter (cm)	7.0	6.5	6.1	7.4	± 6 %

5. Physician labeling

5.1. Why use ultrasound to measure bone?

Ultrasound is a pressure wave that *mechanically* stimulates the bone. The response of the bone to ultrasound takes the form of micro-vibrations, which reflect both the bone's **density** and its **micro-architecture**. The OSTEOSPACE measures the attenuation of these vibrations over a band of

frequencies, i.e., broadband ultrasound attenuation (BUA). BUA has been shown to correlate with fracture risk.

Ultrasound is a technique **free of ionizing radiation**. As such there is no limitation in use for pregnant women

5.2. Is ultrasound a validated technique?

Yes, many important clinical studies have validated the principle of measuring bone density and micro-architecture using ultrasound. Three of them are reference studies:

1. "Osteoporosis: Association of Recent Fractures with Quantitative US Findings," Claus C. Glüer PhD, Stephen R. Cummings MD, Douglas C. Bauer MD, Katie Stone MA, Alice Pressman MS, Ashwini Mathur PhD, Harry K. Genant MD, *Radiology*, vol. 199, Number 3, June 1996.

This study included 4698 elderly women. It reached the following conclusion:

"Quantitative US parameters are strongly associated with risk of fracture and partly independent of BMD. This simple, low-cost, portable, and radiation-free approach may complement bone densitometry in assessing risk of osteoporotic fracture."

2. "Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study," D Hans, P Dargent-Molina, A M Schott, JL Sebert, C Cormier, P O Kotzki, P D Delmas, J M Pouilles, P J Meunier, *The Lancet*, vol. 384, August 24, 1996.

This study, including 5662 elderly women, reached the following conclusion:

"Ultrasonographic measurements of the os calcis predict the risk of hip fracture in elderly women living at home as well as DPXA of the hip does, and the combination of both methods makes possible the identification of women at very high or very low risk of fracture."

3. "Broadband Ultrasound Attenuation Predicts Fractures Strongly and Independently of Densitometry in Older Women," D C Bauer, C Glüer, J A Cauley, T M Vogt, K E Ensrud, H K Genant, D M Black, *Arch Intern Med*, vol.157, March 24, 1997.

In this study, 6189 postmenopausal women were studied. The conclusion was:

"Broadband Ultrasound Attenuation predicts the occurrence of fractures in older women and is a useful diagnosis test for osteoporosis. The strength of the association between BUA and fracture is similar to that observed with bone mineral density."

5.3. Why the calcaneus?

The structure of the calcaneus is mainly trabecular (porous bone) and similar to that of the vertebra, which is a frequent fracture site. The calcaneus has two parallel sides, enabling optimal ultrasound propagation. The calcaneus is also easily accessible, and surrounded by only a small quantity of soft tissues.

The clinical studies quoted above have demonstrated the ability of the measurement at the calcaneus to assess risk of fracture at the hip, as well as at the spine.

5.4. Why gel as a coupling medium?

OSTEOSPACE uses a standard water-soluble ultrasound gel as a coupling method. It enables one to optimize the propagation of ultrasound, obtain a correct signal, and therefore a more reliable and precise examination.

Ultrasound Gel Aquasonic:

Parker Laboratories Inc, 286 Eldridge Road, Fairfield, New Jersey 07004 – Tel : 973-276-9500 or 800-631-8888 ; Fax : 973-276-9510.

For pricing Information call: Kappa Medical Inc, PO Box 11808, Prescott, AZ 86304-1808
Tel: 928-778-0840 ; Fax : 928-776-9250.

For general information: kappamedical@aol.com.

France distributor : SODAP, 1415, avenue Albert-Einstein, 34000 Montpellier.

5.5. Description of OSTEOSPACE parameters

BUA

BUA, or broadband ultrasound attenuation, is the principal parameter of OSTEOSPACE, and is expressed in units of dB/MHz. "Broadband" signifies that a wide range of ultrasound frequencies are used, between 0.2 and 1 MHz. As the ultrasound energy passes through the heel, scattering and absorption by the trabecular bone continuously diminish its intensity, at a rate that depends on its frequency. "Attenuation" is the ratio of the intensity exiting the heel to that entering the heel and BUA describes the way this attenuation varies with frequency.

T-score

The T-score represents the difference between the patient's BUA value and that of the average (age 20 to 39) young normal U.S. Caucasian women, expressed in terms of the standard deviation of the latter population. (See Chapter 21 Glossary in the user's manual for details about the standard deviation.) For T-score the same reference population is used regardless of the age, ethnicity, or gender of the patient. The T-score for BUA is the most important result given by OSTEOSPACE, since the actual definition of osteoporosis, as well as the estimate of fracture risk, is based on this parameter.

Z-score

The Z-score is the difference between the patient's BUA value and that of the average normal subject of the *same* age, gender, and ethnic origin as the patient, again expressed in terms of the standard deviation of this normal population. However, the OSTEOSPACE only provides such a reference database for Caucasian U.S. women.

Precision

The OSTEOSPACE measurement has a coefficient of variation (CV) of 1.31%. CV is the parameter usually used to measure the precision of a device. The coefficient of variation represents the typical variation observed between the measurement and the “true” value, which can be obtained by repeating the same measurement and averaging the results. In a more mathematical way, the coefficient of variation is defined as the ratio of the standard deviation of repeated measurements on the same patient, divided by the mean value.

Knowing the precision of your device allows you to calculate an interval around the measured value which will contain the true value 95% of the time if you were to repeat the measurement over and over. This is referred to as the “95% confidence interval” and is given by $(BUA_0 - 2CV, BUA_0 + 2CV)$, where BUA_0 represents the patient's measured value. For example, if the BUA is 60 dB/MHz, the confidence interval is $60 \pm 1\% \times 60$, i.e. (59.4, 60.6).

6. References / Bibliography

General References:

- [1] Glüer CC, Blake G, Lu Y, Blunt BA, Jergas M, Genant HK. Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. *Osteoporos Int* 1995;5(4):262-70.
- [2] CG Miller, RJ Herd, T Ramalingam, I Fogelman, GM Blake Ultrasonic Velocity Measurement Through the Calcaneus: which velocity should be measured, *Osteoporosis Int* , 1993. 3.31-35
- [3] Glüer CC, How to characterize the ability of diagnostic technique to monitor the skeletal changes. *Journal of Bone and Mineral Research* 1997; 12: S378.